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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Danitol. Review of a Developmental Toxicity Study in Rats.

EPA ID# 39398-16 Project No. 0-1720
Case No. 268241, 268239 Tox. Chem. No. 273H

FROM: John E. Whalan, D.A.B.T., Toxicologist
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John E. Whalan 6-29-92

TO: George LaRocca (PM Team # 15)
Registration Division (H7505C)

for **THRU:** Roger L. Gardner, Section Head Pamela M. Hurley 6/30/92
Section 1, Toxicology Branch I
Health Effects Division (H7509C) R. G 7/15/92 HB 7/17/92

In conjunction with a label amendment to add outdoor uses, Valent U.S.A. submitted a Developmental Toxicity study in rats. It replaces a previous study (Hazleton Project No. 343-122, April 22, 1980) which was found to have numerous deficiencies that made it impossible to define doses. The study was downgraded to **Core Supplementary**.

The new study, which is classified **Core Guideline**, satisfies data requirement 83-3 for a developmental toxicity study. No developmental toxicity was observed at 10 mg/kg/day (the highest dose tested), a dose that was lethally neurotoxic to the dams.

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Reviewed by: John E. Whalan JW 3-20-92
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Section I, Tox. Branch I (IRS) (H7509C)

GUIDELINE: 83-3

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity Study in Rats

MRID NO.: 415259-03

TOX. CHEM. NO.: 273H

TEST MATERIAL: S-3206 TG (Lot No. 70711; 91.9% a.i.; brown solid)

SYNONYMS: Danitol technical

STUDY NUMBER(S): HLA 343-216

SUBMITTED BY: Valent U.S.A. Corporation on behalf of Sumitomo Chemical Co. Ltd.

TESTING FACILITY: Hazleton Laboratories America, Inc.

TITLE OF REPORT: Rat Teratology Study with S-3206

AUTHOR(S): Sandra L. Morseth

REPORT ISSUED: March 13, 1990

CONCLUSIONS: Female CDF®(F-344)/CrlBR rats were dosed by gavage on gestation days 6-15 at 0 (corn oil control) 0.4, 1.5, 2.0, 3.0, 6.0, and 10.0 mg/kg/day. No developmental toxicity was observed at a dose that was lethally neurotoxic to the dams. The defined doses are as follows:

Maternal NOAEL = 6 mg/kg/day
Maternal LEL = 10 mg/kg/day (death, moribundity, ataxia, sensitivity to external stimuli, spastic jumping, tremors, prostration, convulsions, hunched posture, squinted eyes, chromodacryorrhea, and lacrimation)
Developmental NOAEL >10 mg/kg/day

STUDY CLASSIFICATION: This study, which is classified **Core Guideline**, satisfies data requirement 83-3 for a developmental toxicity study. This study received Quality Assurance review. Formulation homogeneity results were not reported.

PROTOCOL: A total of 78 male and 262 sexually mature female CDF®(F-344)/CrlBR rats (10-12 weeks old) were individually housed in stainless steel cages. Food and water were available *ad libitum*. Seventy-eight males were mated - one male and one female per cage. When mating was confirmed by the presence of a vaginal plug or sperm, the females were replaced by another female until the required number of mated females was attained. Confirmation of mating defined gestation day 0.

The weight range of the females on gestation day 0 was 148 to 197 g. The mated females were randomly assigned to 7 groups of 30 rats. They were dosed on gestation days 6-15 by oral intubation at the rate of 1 ml/kg at 0 (vehicle control), 0.4, 1.5, 2.0, 3.0, 6.0, and 10.0 mg/kg/day. The vehicle was corn oil. The test article was analyzed for stability, homogeneity, and dose concentration.

Clinical signs were recorded at least once daily, and more often if signs were observed. Body weights and food consumption were recorded on gestation days 0, 6, 8, 11, 15, 16, and 20. On gestation day 20, all females were sacrificed by carbon dioxide asphyxiation and exsanguination. They were grossly examined, and the uterus from each gravid female was weighed and examined for live and dead pups, implantation sites, resorptions, and abnormalities. The number of corpora lutea was also recorded.

The fetuses were sexed, weighed, and examined for external abnormalities. Approximately one-third of the fetuses from each litter were preserved in Bouin's fixative, and processed by the Wilson technique for visceral examination. The remaining fetuses were eviscerated, fixed, dehydrated, macerated, stained with 0.5% sodium hydroxide and Alizarin Red S, cleared in 50% glycerin, and then evaluated for skeletal variations and malformations.

RESULTS: Analyses of the 0.4, 2.0, and 10.0 mg/kg/day formulations showed the test article to be stable over a 10-day period. Dose concentration analyses were within 10% of nominal.

In the high-dose group, 6 dams died between gestation days 7 and 13, and one was sacrificed moribund on day 8 because of convulsions and prostration. This left 23 dams which survived to gestation day 20 compared to 30 dams in all the other groups. Neither death nor moribundity were found in the other groups.

Clinical signs seen in the majority of high-dose dams included ataxia, sensitivity to external stimuli, spastic jumping, and tremors. These signs were most severe 2 hours after dosing, and during the first days of dosing, although sensitivity to external stimuli persisted throughout the dosing period. Prostration, convulsions, hunched posture, and squinted eyes were each seen in one high-dose dam. Chromodacryorrhea and lacrimation, which occurred sporadically in all other groups, became dose-related in the high-dose.

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Food consumption was decreased 17% in the 10 mg/kg/day group, and 11% in the 6.0 mg/kg/day group between gestation days 6 and 8, but was comparable in all groups at other times. Body weight gain was also decreased in these two dose groups between gestation days 6 and 8. Over the course of the study, however, body weights, gravid uterus weights, corrected body weights (i.e. carcass weights), and food consumption were similar in all groups. The corrected body weight from day 0 for the high-dose dams was 4% less than the controls, and the net weight change (corrected weight minus day 0 body weight) was 38% less than the controls. There were no dose-related gross lesions in the survivors or in the seven animals that died on study.

Table 1 presents the maternal observations. These data show that all groups were comparable with regards to fertility, fecundity, the number of corpora lutea, implantations, resorptions, live fetal body weights, and sex ratios; and the lack of abortions, dead fetuses, and late resorptions. The only anomalous value in this table is the number of rats found dead in the high-dose group, as previously discussed.

None of the fetuses had any external variations or malformations. The incidences of soft tissue variations and malformations were few and not dose-related. Incomplete and assymetrical ossification variations were slightly more frequent in the dosed groups than in the controls, but there was no dose-relationship. There were no skeletal malformations. Photocopied study tables of soft tissue and skeletal variations and malformations are attached.

DISCUSSION: Maternal toxicity was clearly attained as evidenced by the six deaths and one moribund sacrifice in the high-dose group, and the neurologic signs observed in this and other groups. Although food consumption and body weight gain were decreased between gestation days 6 and 8, the effect was short lived and was probably due to neurotoxicity rather than metabolic or palatability factors. No developmental toxicity was expressed at the doses tested. Thus, the defined doses are as follows:

Maternal NOAEL = 6 mg/kg/day
Maternal LEL = 10 mg/kg/day (death, moribundity, ataxia, sensitivity to external stimuli, spastic jumping, tremors, prostration, convulsions, hunched posture, squinted eyes, chromodacryorrhea, and lacrimation)
Developmental NOAEL >10 mg/kg/day

An earlier study (Hazleton Laboratories America, Inc. Project No. FT-01-0031; April 22, 1980), which has since been downgraded to Core Supplementary because of numerous deficiencies, identified fetal anomalies of edema, hydrocephaly, gastroschisis, dilated renal pelvis, and lagging ossification of the skull, rib cage, vertebral column, and pelvic girdle. Of these lesions, only delayed ossification of the skull, vertebral column, and pelvic girdle were observed in this study, and none were of significant incidence.

Table 1: Summary of Selected Maternal Observations

Observation	Doses (mg/kg/day) 0	0.4	1.5	2.0	3.0	6.0	10
Number assigned	30	30	30	30	30	30	30
Pregnant dams	30 (100%)	28 (93%)	28 (93%)	29 (97%)	28 (93%)	29 (97%)	27 (90%)
Rats found dead	0	0	0	0	0	0	6
Abortions	0	0	0	0	0	0	0
Dams with no viable fetuses	0	0	0	1	0	0	0
Pregnant dams @ day 20	30 (100%)	28 (93%)	28 (93%)	29 (97%)	28 (93%)	28 (93%)	21 (70%)
Corpora lutea/dam	11.6	12.1	11.6	11.9	11.4	11.9	12.0
Implantations/dam	8.8	10.0	9.0	9.7	9.0	9.7	9.9
Dead fetuses (total)	0	0	0	0	0	0	0
Live fetuses/litter	8.5	9.6	8.6	8.9	8.8	9.1	9.5
% Male fetuses	51%	51%	45%	59%	52%	48%	53%
Resorptions/dam	0.3	0.4	0.4	0.8	0.2	0.6	0.3
Early	0.3	0.4	0.3	0.8	0.2	0.6	0.3
Late	0	0	0.1	0	0	0	0
Live fetal body weights (g, total)	3.04	2.99	3.09	3.04	3.03	3.01	2.97

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